TABLE 1. Frequency for the top five ICD-9 and ICD-10 codes for the multiple causes of death and for codes that generated further investigation

Code	Grouping or frequency	Number
ICD-9 morbidity/mortality codes for deaths between 1978 and 1998		
ICD-9	*Five most frequent grouping of codes (total diagnosis codes 696 from 252 decedents*)*	
420.0-429.9	Other forms of heart disease	67
410.0-414.9	Ischemic heart disease	58
200.0-208.9	Malignant neoplasms of lymphatic and hematopoietic tissue	45
570.0-579.9	Other diseases of digestive system	37
280.0-289.9	Diseases of blood and blood-forming organs	34
	Frequency of codes that generated further investigation†	
046.1	CJD	0
310.9	Specific nonpsychotic mental disorders following organic brain damage, unspecified	1
331.9	Other cerebral degenerations, unspecified	0
341.9	Other demyelinating diseases of central nervous system, unspecified	0
348.8	Other conditions of brain	0
ICD-10 morbidity/mortality codes for deaths for 1999 through present		
ICD-10	*Five most frequent grouping of codes (total diagnosis codes 182 from 77 decedents*)*	
I30.0-I51.9	Other forms of heart disease (e.g., cardiac arrest, congestive heart failure, endocarditis)	21
I20.0-I25.9	Ischemic heart disease	18
N17.0-N19.9	Renal failure	15
I60.0-I69.9	Cerebrovasular disease	12
I10.0-I13.9	Hypertensive disease	8
	Frequency of codes that generated further investigation†	
A81.0	CJD	0
A81.2	Progressive multifocal leukoencephalopathy	0
A81.9	Atypical virus infection of central nervous system, unspecified	0
B94.8	Sequelae of other specified infectious and parasitic diseases	0
E85.2	Heredofamilial amyloidosis, unspecified	0
F03	Unspecified dementia	3
G20	Parkinson's disease	1
G30.0	Alzheimer's disease with early onset	0
G30.9	Alzheimer's disease, unspecified	1
G31.8	Other specified degenerative diseases of nervous system	0
G47.0	Disorders of initiating and maintaining sleep	0
G90	Disorders of the autonomic nervous system	0
G93.3	Postviral fatigue syndrome	0
G93.4	Encephalopathy, unspecified	0
G93.9	Disorder of brain, unspecified	0
G96.9	Disorder of central nervous system, unspecified	0
G98	Other disorders of nervous system, not elsewhere classified	0
R99	Other ill-defined and unspecified causes of mortality	0

* Mean number of multiple cause of death codes listed per decedent is 3 for both ICD-9 and ICD-10.
† Mean age at death for those decedents that triggered further investigation was 79.5 years (range, 64-101 years).

these diagnoses were autopsy and/or biopsy confirmed by examination of brain tissue. Of these 36 CJD donors, 34 (94%) were identified as sporadic CJD, 1 as familial CJD (E200K), and 1 as iatrogenic CJD.

These 36 donors donated blood in 16 states in the United States between 1970 and 2006. The mean age of these donors at onset of their CJD was 60 years (range, 39-74 years). The mean of reported donations made by the donors was 20 (range, 1-76). Not all of the donations yielded an enrolled recipient. Of the units linked to identified study recipients, red blood cells (238 units) were the most commonly received component, followed by platelets (75 units), and plasma (49 units) with the remaining units being other types of components such as whole blood, cryoprecipitate, and granulocytes (35 units).The transfusion service did not report the type of component received for 41 of the recipients.

Study recipients and the results of their follow-up

A total of 436 recipients were included in this lookback. Their median age at transfusion was 66.1 years (range, 4 days to 99 years). They received transfusions in 30 different states between 1970 and 2006.

As of the end of December 2006, 329 recipients (75.4%) were deceased, 91 (20.9%) were alive, and 16 (3.7%) were lost to follow-up. For those who died, the median age at death was 70.5 years (range, 8 months-101 years). None died with a diagnosis of CJD. The top five causes of death for the reported combined underlying cause and multiple causes of death groupings are listed in Table 1; ICD-9 codes were used for deaths occurring before 1999 and ICD-10 codes were used for deaths occurring for 1999 through present and the complete list can be found in Table 1. On average, the decedents had three multiple causes of death

TABLE 2. Distribution of recipients by vital status and the interval between their transfusion and their donor's onset of CJD

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Alive	Deceased	Lost to follow-up	Total
≤12	17	44	5	66 (15.1%)
13-24	5	32	3	40 (9.2%)
25-36	12	50	1	63 (14.5%)
37-48	5	35	0	40 (9.2%)
49-60	8	43	0	51 (11.7%)
61-72	15	26	0	41 (9.4%)
≥73	29	99	7	135 (30.9%)
Total	91 (21%)	329 (75%)	16 (4%)	436 (100%)
Person-years followed	1199.25	832.25	64.5	2096.00

TABLE 3. Distribution of recipients by years of posttransfusion survival and the interval between transfusion and onset of CJD in donor

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Posttransfusion survival (years)									
	≤4	5	6	7	8	9	10	≥11	≥5, subtotal	Total
≤12	47	2	0	0	7	1	3	6	19	66
13 to 24	31	0	0	1	1	1	2	4	9	40
25 to 36	51	0	2	1	0	0	1	8	12	63
37 to 48	27	0	2	2	0	1	2	6	13	40
49 to 60	36	1	3	2	0	1	0	8	15	51
61 to 72	19	1	3	0	2	2	2	12	22	41
≥73	81	3	1	5	4	4	1	36	54	135
Total	292	7	11	11	14	10	11	80	144	436

listed. Codes that triggered further investigation were 310.9, F03, G20, and G30.9 and occurred six times. Review of each of the six death certificates verified that none included any mention of prion diseases. The mean age of the six decedents was 79.5 years (range, 64-101 years; Table 1). Almost half (49%) of the recipients died within the first year after transfusion. The 2006 NDI results indicated that 91 recipients (all but 2 were adults) were still alive at the end December 31, 2006. Of these 89 adults, AutotrackXP subsequently provided further evidence that at least 85 percent of them were alive.

Recipients in the study were documented to have survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor (Table 2). The 329 deceased recipients contributed 832.25 of these person-years and the 91 recipients who were alive as of December 2006 contributed 1199.25 person-years. The remaining 16 recipients who were lost to follow-up had contributed 64.5 person-years.

A majority (60%) of the 436 recipients in this study received blood and components from CJD donors that were donated 60 months or less before their onset of CJD (Table 2). A total of 66 recipients received their units within 12 months or less of the donor's onset of CJD. Of the 260 recipients who received blood from donors 60 months or less before their donor's onset of CJD, 47 (18%) were still alive as of 2006.

Approximately one-third of the recipients survived 5 or more years after transfusion (Table 3). Within this group of long-term survivors, 68 recipients (46.8%) received blood that had been donated 60 months or less before onset of CJD in the donor.

We compared the risk associated with receipt of blood components donated 60 months or less before the onset of the prion disease in the CJD donors in the United States and the vCJD donors in the United Kingdom. Whereas in the United States, no case of CJD was identified among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset, in the United Kingdom 3 cases of vCJD (14%) were identified among 21 long-term surviving recipients of the blood components donated by the vCJD donors ($p = 0.012$, Fisher's exact test).

DISCUSSION

This study evaluates the risk of transfusion transmission of CJD in US blood recipients and compares the risk to that reported for vCJD in the United Kingdom. Overall, the US recipients survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor. No recipient was found to have been diagnosed with CJD. These results indicate that for the period studied, the risk, if any of transfusion transmission of CJD by CJD donors is significantly lower than the risk of transfusion transmission of vCJD by vCJD donors.

Although the incubation period for prion diseases can be very long, about 30 years or longer as observed

when environmental exposures can be reasonably estimated (e.g., Kuru, dural graft-associated CJD, and pituitary hormone-associated CJD), it is noteworthy that at least one case for each of these prion diseases has been observed within 10 years of an exposure. The present plan for evaluating transfusion transmission of CJD is to continue the current surveillance efforts and to continue to identify new recipients for at least another 5 years.

There could be a variety of reasons for not seeing a case of CJD in our recipient population. One of the most likely reasons is that CJD may not be transmitted by blood transfusion, unlike its variant counterpart. If the agent that causes CJD were present in human blood, its concentration might be too low to transmit an infection by the intravenous route. It is also possible that this study has not yet included enough donors and recipients to observe an infection or followed up on the study recipients long enough for them to have completed their incubation period.

The observation of zero cases of CJD among recipients in this study is consistent with the considerable additional data in the medical literature on the risk of transfusion transmission of human prion diseases that has recently been reviewed.[8] In addition to the UK TMER study, we are aware of a German lookback investigation of one blood donor who died of CJD. The donor had 27 definite recipients and 8 probable recipients (total, 35). None of the deceased recipients died from dementia or neurologic causes. Of the 14 who were alive at publication, none exhibited signs of dementia; the longest period of follow-up was 21 years.[14]

Through 2007, the proportion of vCJD cases among the long-term surviving recipients who received blood from a vCJD donor 60 months or less before onset of the donors' illness was 14 percent in the United Kingdom. In contrast, the present study identified no case of CJD among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset. In addition, the smaller UK study of blood components donated by CJD donors in the United Kingdom revealed no transfusion transmissions of CJD. Thus, the results of the present study in combination with the results from the TMER study in the United Kingdom strongly support the conclusion that the risk, if any, associated with receipt of blood components from CJD donors is significantly lower than that associated with receipt of blood components from vCJD donors.

The limitations of this study include the fact that 15 (42%) of the CJD donors enrolled in this study did not have their diagnosis confirmed neuropathologically. The CJD illness of each of these 15 donors was diagnosed by a neurologist and at least 11 of these donors had an electroencephalogram characteristic of CJD and/or a positive cerebrospinal fluid test for the neuron-specific enolase or 14-3-3 proteins. Nevertheless, it is possible that not all the recipients received blood from a true CJD donor.

Another limitation of this study is that we relied upon the US multiple cause of death data to identify CJD in recipients. The sensitivity of such data was assessed by a CDC study conducted in 1996, shortly after vCJD was first announced in the United Kingdom. Although this latter study did not allow for sufficient time for complete filing of all death records, it nevertheless found that the sensitivity of the death records compared to very active, alternative surveillance efforts was 86 percent.[4] In addition to this study, Davanipour and colleagues[20] found the false-positive rate of the death certificates to be 8.3 percent.

Assessment of risks of blood-borne transmission of diseases with potentially long latent periods is inherently limited by the poor survival of transfusion recipients. In the present study, for example, approximately 26 percent[21] of the recipients were alive 10 years after transfusion. Although this survival rate is low, it is consistent with another report of lookback investigations in which only 26 percent of the recipients had survived 10 or more years posttransfusion. Lookback investigations may be more inclined to have lower posttransfusion survival rates because they overrepresent recipients that receive multiple transfusions.[22,23] This relatively low survival rate contributes to the limited statistical power of the present study despite its being the largest study of its kind reported to date to assess the risk of transfusion transmission of CJD. Further detection and enrollment of donor/recipient clusters will continue to increase the power, and, if recipients remain free of CJD, will continue to provide the most direct evidence for the absence of CJD transmission by transfusion. Finally, another limitation encountered in this and other lookback investigations is the increasing difficulty in obtaining identifying information on all recipients. As hospital personnel have become more concerned about remaining in compliance with the federal medical privacy rule of the Health Insurance Portability and Accountability Act (HIPAA), our ability to obtain patient information has been reduced.

In addition to providing public health surveillance data on CJD and blood transfusions, our study provides important evidence demonstrating that compared to vCJD donors, CJD donors pose much less of a risk, if any, to blood safety. Precisely why this difference exists, however, is not fully understood, although clearly CJD and vCJD are different prion diseases. They are most prevalent in different age groups, their pathology and etiologic prion disease agents differ, and they are characterized by a different pattern and duration of clinical signs and symptoms.[5,8] As pointed out by the authors of the TMER study, the observed increased lymphoreticular involvement in vCJD compared to CJD is consistent with an increased transfusion-transmissibility of vCJD.[7,24] Further research may shed additional light on the pathophysiologic

mechanisms that account for the greater transfusion transmissibility of vCJD compared to CJD.

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研究報告の概要

Health Protection Agency による扁桃腺組織の大規模な研究結果によれば、vCJD の無症候の人数の最新の推定値は非常に低いままである（2009 年 5 月 22 日）。
63,000 のサンプルのいずれにも vCJD と関連している異常プリオン・タンパク質の証拠は見つからなかった。
2004 年、Health Protection Agency は抽出された扁桃腺から vCJD と関連しているプリオンタンパク質をさがすことによって、無症候性 vCJD の保有率を確定するために National Anonymous Tissue Archive（NATA）を開始した。
扁桃腺は一度感染すると vCJD プリオンが蓄積する部位の一つである（その他の部位は、脾臓、虫垂、リンパ節、脊椎及び脳）。
集団での vCJD 保有率を認識することは、集団に対するリスクのレベルを決定する、感染の影響を限定する、あるいは疾患を発病する可能性がある人々のために健康管理介入を計画するために重要である。
調査はすでに 63,000 の扁桃腺組織の収集と解析を行っており、合計 100,000 まで検体を収集し続ける予定である。
当初 100,000 のサンプルのうちの最高 50 検体が異常プリオン・タンパク質を含むことが推定されたが、現在までのところ陽性サンプルは一つもなかった。調査結果は集団中の無症候性の vCJD は予想より少ない可能性があることを示唆する。

報告企業の意見	今後の対応
2004 年に HPA は、摘出された扁桃腺における vCJD 関連プリオン蛋白質を検出することにより、無症候性 vCJD 有病率を確定するために NATA を開始したが、無症候性 vCJD 症例は当初予想されていたよりも少ない可能性があることを示唆する報告である。 血漿分画製剤は理論的な vCJD 伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を 2003 年 5 月から添付文書に記載している。2009 年 2 月 17 日、英国健康保護庁(HPA)は vCJD に感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD 異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内での BSE の発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは 1999 年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1) 略
1) 略
2) 現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

Protecting people
Preventing harm
Preparing for threats

Latest research into prevalence of vCJD consistent with findings of existing studies

22 May 2009

Latest estimates of the number of people asymptomatic for variant Creutzfeldt-Jakob disease (vCJD) in the population remain very low, according to results from a large scale study of tonsil tissue by the Health Protection Agency, published in today's BMJ (Friday 22nd May 2009).

No evidence of the abnormal prion protein associated with vCJD was found in any of the 63,000 samples analysed.

In 2004, the Health Protection Agency launched the National Anonymous Tissue Archive (NATA) to determine prevalence of asymptomatic vCJD in the population, by looking for the prion protein associated with vCJD in extracted tonsils. The tonsils are one of the sites in the body where, once infected, vCJD prions can accumulate (other sites include the spleen, appendix, lymph nodes, spinal cord and brain).

Awareness of the prevalence of vCJD in the population is important to determine the level of risk to the population and to limit the impact of infection or plan healthcare interventions for people who may develop the disease.

The survey has already involved collection and analysis of 63,000 discarded tonsils, and will continue on until a total of 100,000 samples of leftover tonsil tissue have been examined.

When the archive was established it was estimated that up to 50 of the 100,000 samples could contain the abnormal prion protein, however so far none of the samples are positive.

The findings suggest there may be fewer undetected asymptomatic cases of vCJD in the population than were previously expected. However, only by testing a larger number of tonsils and continuing and expanding on the current survey, will scientists be confident that the prevalence is lower than earlier estimates.

Dr Jonathan Clewley, an expert on vCJD at the Health Protection Agency, said: "It may be that we have seen the worst of vCJD already, although we need to keep vigilant and implement appropriate public health measures to prevent any possible secondary spread of disease.

"Estimating the prevalence of people who are carrying vCJD unknowingly is important in guiding our public health response to this disease and ensuring all necessary precautions are taken to reduce this risk of further transmission of the agent through surgical operations and other healthcare settings.

"Further studies are planned to strengthen prevalence estimates, these will involve large scale anonymous tissue surveys, and continuation with the testing of tonsil specimens especially in the older age groups."

Ends

Notes to editors

1. The National Anonymous Tissue Archive (NATA) is managed by the CJD Team at the Health Protection Agency and the Transmissible Spongiform Encephalopathies Unit for the Department of Health.

2. The findings are published in the BMJ paper; *Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: a cross-sectional opportunistic survey,* J Clewley *et al. BMJ* 2009; 338: b1442.

3. 63,007 samples were taken, of which 12,763 were from the birth cohort where most cases had arisen (1961-1985), 19,908 were in the 1985-1995 cohort who would have also been exposed to BSE from infected meat or meat products. None of the samples that were investigated by immunohistochemistry or immunoblotting were positive for the presence of PrP^{CJD}.

4. The archive is completely anonymous; after tonsils are removed, they are separated from any identifiable patient